Editorial

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Published in:
Current Pharmaceutical Design

Publication date:
2006

Editorial: PET and SPECT in Drug Evaluation and Drug Design: Novel Techniques

This is the fourth issue of Current Pharmaceutical Design discussing applications of PET and SPECT in drug development. The initial issue (Vol. 6, No. 16, 2000) described methods for measuring the deposition, biodistribution and pharmacokinetics of drugs including their interactions with certain targets. The second issue (Vol. 8, No. 16, 2002) focused on the interface between nuclear medicine and molecular biology. A third issue (Vol. 10, No. 13, 2004) identified novel areas where molecular imaging could contribute to drug design: anti-angiogenic therapy, modulation of programmed cell death, suppression of beta-amyloid plaque formation, inhibition of cerebral acetycholinesterase and of P-glycoprotein-mediated drug transport in the blood-brain barrier, downregulation of beta-adrenoceptors by antidepressants. The current issue gives an overview of novel targets within the human brain for which radioligands have recently been developed.

Drs. Ding, Lin and Logan [1] from Brookhaven National Lab (Upton, NY, USA) describe the efforts of several research groups to visualize the cerebral norepinephrine transporter (NET). It has proven quite difficult to develop suitable radioligands for this particular target, although dopamine and serotonin transporter ligands are readily available.

The development of (S,S)-[^{11}C]methylreboxetine is a breakthrough, since this compound displays a much greater *in vivo* selectivity and specifity than any other existing NET radioligand. Since the writing of this review, a fluorinated derivative of reboxetine has been reported to show even better properties[1]. The availability of (S,S)-[^{11}C]methylreboxetine may allow researchers to probe the contribution of the NET system to specific brain disorders, such as attention-deficit hyperactivity disorder (ADHD), substance abuse, Alzheimer's disease and Parkinson's disease, and to monitor NET occupancy during treatment with antidepressant drugs.

Dr. De Vries [2] from the University of Groningen (The Netherlands) focuses on another difficult target. Expression of cyclooxygenase-2 (COX-2) within tissues is transiently induced during inflammation and in brain disorders like Alzheimer's disease and Parkinson's disease. The enzyme is also overexpressed in a variety of tumors, and related to angiogenesis, tissue invasion, metastasis and apoptosis. A noninvasive method to monitor COX-2 expression may provide novel insights in the role of COX-2, particularly within the CNS where repetitive sampling is not possible. Two radiolabeled COX-2 inhibitors show specific binding within brain, but the high lipophilicity of these compounds results in a high background signal. However, it is possible to study the effects of COX-2 inhibitors on blood flow, glucose metabolism and apoptosis with PET.

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[1]Schou M, Halldin C, Pike VW, Mozley PD, Dobson D, Innis RB, Farde L, Hall H. (S,S)-[18F]FMeNER-D2 is superior to (S,S)-[11C]MeNER as a positron-emitting radioligand for imaging norepinephrine transporters in the post mortem human brain. Eur J Nucl Med Mol Imag 32 (Suppl 1): S44, 2005.

Drs. Hashimoto and Ishiwata [3] from Chiba Graduate University of Medicine and the Tokyo Metropolitan Institute of Gerontology (Japan) discuss the application of sigma receptor ligands as therapeutic drugs and as radiopharmaceuticals. Sigma receptors are novel targets for the therapeutic treatment of schizophrenia, depression, cognitive impairment, stroke-induced ischemia, and cocaine addiction. Sigma-2 agonists are novel therapeutic drugs for the treatment of cancer. Radioligands for sigma-1 and sigma-2 receptors have been developed by various research groups. PET and SPECT studies with these radioligands may provide insight in the role which sigma receptors play in pathophysiology. Such studies also allow measurement of sigma receptor occupancy by therapeutic drugs, and will be of prognostic relevance in cancer patients.

Drs. Horti and Villemagne [4] from Johns Hopkins Medicine (Baltimore, USA) and the University of Melbourne (Australia) review the development of radioligands for imaging of nicotinic acetylcholine receptors (nAChR) within human brain. For a variety of reasons, cerebral nAChR are a difficult target. They are expressed at much lower densities than e.g. dopamine receptors. First-generation ligands (epibatidine analogs) were very toxic. Second-generation radioligands (A-85380 analogs) showed a better toxicity profile but slow brain kinetics and moderate signal-to-noise ratios. Ligands with better kinetics have been developed but not yet characterized *in vivo*. If they prove suitable, such ligands can be used to elucidate the role of nAChR in (patho)physiology, to monitor response to cholinergic drugs in Alzheimer's disease and to correlate therapeutic response to nAChR occupancy.

Finally, Dr. Eckelman [5] from Molecular Tracer, LLC (Bethesda, MD, USA), reviews imaging studies on muscarinic receptors (mAChR) within the central nervous system. Initial studies used radioligands with a very high affinity. Such ligands reached high target-to-nontarget ratios but quantification of binding sites was difficult. Second-generation ligands have slightly less affinity. These allow quantification of binding sites, and, in some cases also measurement of the amount of endogenous acetylcholine. It is possible to study the interaction of drugs with mAChR, to assess changes of mAChR in mild to moderate Alzheimer's disease and in clinically normal subjects genetically predisposed to Alzheimer dementia. Monitoring the effects of therapy in such subjects will probably be possible in the future.

A common subject which is discussed by several authors is the profile of an ideal PET tracer. This item returns in the contributions of Ding *et al*. (section II), of Horti & Villemagne (sections II and X), and of Eckelman. These discussions are of general relevance and not only important for a particular imaging application.

In closing, I would like to thank all contributors for writing these excellent reviews.

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